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Synthesis of 4-substituted arsabenzenes

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ABSTRACT

It had been assumed that heterocycles similar to pyridine but containing heavier elements do not exist. This situation has changed radically during the last two decades, when several heterobenzene compounds (i.e. arsabenzene, phosphabenzene, stibabenzene and bismabenzene) were synthesized. This paper reviews the latest work on the synthesis of 4-substituted arsabenzenes.

INTRODUCTION

The resemblance between benzene and pyridine in terms of structure, spectra and chemical stability is well known. This similarity indicates that replacement of a methine group of benzene by an isoelectronic nitrogen does not disrupt its aromatic character.

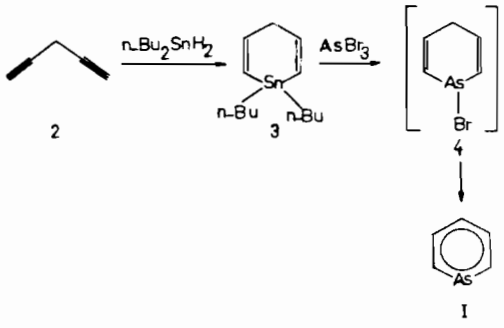
The synthesis of new heteroaromatic compounds, the homologues of pyridine EC_5H_5, E: P, As, Sb, Bi were reported in the early 70's (Ashe 1971a & b). Phosphabenzene (PC_5H_5) and arsabenzene (AsC_5H_5) were found to be air sensitive, but were distillable liquids and could be handled easily under an inert atmosphere. Stibabenzene (SbC_5H_5) was highly labile and polymerized at room temperature, whereas bismabenzene (BiC_5H_5) was only detected spectroscopically and via chemical trapping (Ashe & Gordon 1972). Among these heterobenzenes, phosphabenzene and arsabenzene have been thoroughly studied in the last decade (Ashe 1978; Tzschach & Heinicke 1978; Quin 1981; Ashe 1982; Maerkl *et al.* 1984). The physical and chemical properties of arsabenzene are very similar to those of benzene itself.

SYNTHESIS

1. Synthesis of arsabenzene

Arsabenzene (1) was easily prepared as shown in Scheme 1. 1,4-Pentadiyne (2) was allowed to react with di-n-butyltin dihydride to give 1,1-di-n-butyl-1-stannacyclohexa-2,5-diene (3) which upon treatment with arsenic tribromide gave 1-bromo-1-arsacyclohexa-2,5-diene (4). Compound 4 readily eliminated hydrogen

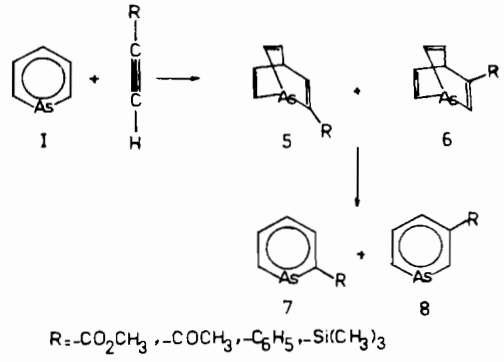
bromide either on treatment with 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) or upon distillation (Ashe 1971a & b).



Scheme 1

2. *Synthesis of substituted arsabenzenes*

2-Substituted arsabenzenes have been prepared using 1-substituted-1,4-pentadiynes in place of 2(Ashe & Chan 1979). In addition, 2- and 3-substituted arsabenzenes have also been prepared by the Diels-Alder reaction of arsabenzene with different dienophiles such as mono-substituted acetylenes (Scheme 2) (Ashe & Friedman 1977; Abu-Orabi & Ashe 1986, 1987).



Scheme 2

Also, it was reported that 2-aryl-, 2,6-diaryl- and 2,4,6-tri-arylarsabenzenes were prepared via the protonation of 4-hydroxy-1,4-di-hydroarsabenzenes (Maerkl *et al.* 1983).

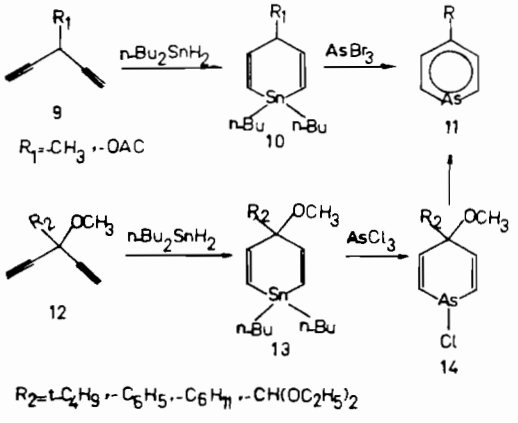
3. *Synthesis of 4-substituted arsabenzenes*

The synthetic methods for the preparation of 4-substituted arsabenzenes can be divided into three classes:

A. Via 3-substituted-1,4-pentadiynes.

Arsabenzene was synthesized by the reaction of 1,4-pentadiyne with di-n-butyltin dihydride (Scheme 1). In the same manner, the reaction of 3-substituted-1,4-pentadiynes (9) with di-n-butyltin dihydride followed by

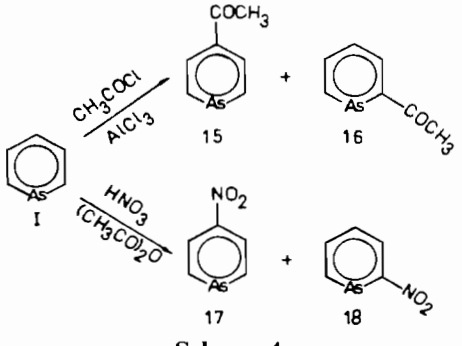
arsenic trihalides gave 4-substituted arsabenzenes (11) (Scheme 3) (Ashe & Chan 1975; Maerkl *et al.* 1975; Hodges *et al.* 1985). A modification of this method allowed the synthesis of a variety of 4-substituted arsabenzenes. Thus, 3-substituted-3-methoxy-1,4-pentadiynes (12) were converted to the corresponding 1,4-dihydrostannabenzenes (13), which on treatment with arsenic trichloride gave 4-substituted arsabenzenes (11) after losing the elements of methyl hypochlorite (Scheme 3) (Maerkl & Kneidl 1973, 1974).



Scheme 3

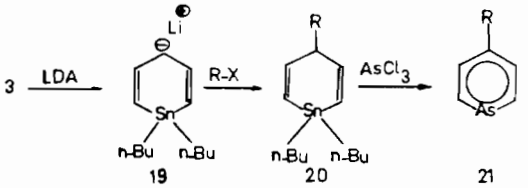
B. Via electrophilic aromatic substitution.

The chemical and physical properties of arsabenzenes are very similar to those of benzene. Therefore, one might expect that arsabenzene can undergo electrophilic aromatic substitution reactions. Indeed, it was reported that arsabenzene can undergo electrophilic aromatic substitution at the 2- and 4-positions. However, from a synthetic standpoint, only Friedel-Crafts acylation took place in preparatively satisfactory yield (Ashe *et al.* 1978). Nitration gave only a low yield with arsabenzene, while the conditions for halogenation and sulfonation destroy arsabenzene (Scheme 4) (Ashe *et al.* 1981).



Scheme 4

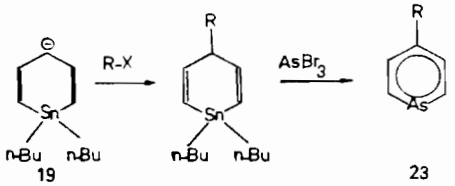
C. Via direct functionalization of 1,1-di-n-butyl-1-stannacyclohexa-2,5-diene.
The diallylic protons of 1,1-di-n-butyl-1-stannacyclohexa-2,5-diene (3) are sufficiently acidic to be deprotonated by a suitable base. Thus, treatment of compound 3 with lithium diisopropylamide (LDA) gave lithium stannacyclohexadienide (19). Quenching (19) with alkyl halides (R-X) gave 4-alkyl-1,1-di-n-butyl-1-stannacyclohexa-2,5-dienes (20), which were easily converted in the usual manner to the corresponding 4-alkylarsabenzenes (21) (Scheme 5) (Jutzi & Baumgartner 1978; Ashe *et al.* 1982).



Scheme 5

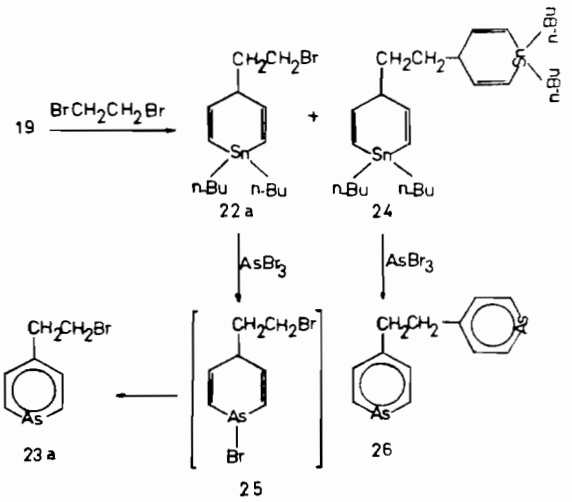
The two previous methods of preparing 4-substituted arsabenzenes seem very limited due to the problem of opening the arsabenzene ring under the acidic condition of the electrophilic aromatic substitution reactions and also due to the limited number of available 3-substituted-1,4-pentadiynes. Moreover, 1,1-di-n-butyl-1-stannacyclohexadiene can be easily prepared in a reasonable yield and they have a good shelf life. Therefore, compound 3 seems an ideal precursor for 4-substituted arsabenzenes. However, the scope of a variety of substituents with manipulatively useful functional groups was explored recently (Abu-Orabi 1982).

Stannacyclohexadienide (19) was alkylated with a variety of primary alkyl halides bearing different functional groups and then followed by treatment with arsenic tribromide to give the corresponding 4-substituted arsabenzenes (23) with an average yield of 50% (Scheme 6) (Ashe & Abu-Orabi 1983).



Scheme 6

Quenching the anion (19) with excess of 1,2-dibromoethane at 25°C afforded 1,1-di-n-butyl-4-(β-bromoethyl)-1-stannacyclohexa-2,5-diene (22a) in 20% yield. The low yield of Compound 22a was attributed to the formation of non-distillable material (24) which on treatment with arsenic tribromide formed 1,2-bis(4-arsabenzene)ethane (26) in 70% yield (Scheme 7). This compound was identical to that reported earlier (Maerkl & Rampal 1977). In order to circumvent the formation of Compound 24, the reaction was repeated with inverse order of addition of dibromoethane. After the anion (19) was formed it was transferred to a solution of dibromoethane in tetrahydrofuran at ice temperature; the yield of Compound 22a was improved to more than 40%. Reaction of 22a with arsenic tribromide in the usual manner gave 4-(β-bromoethyl) arsabenzene (23a) in 82% yield (Abu-Orabi 1982).

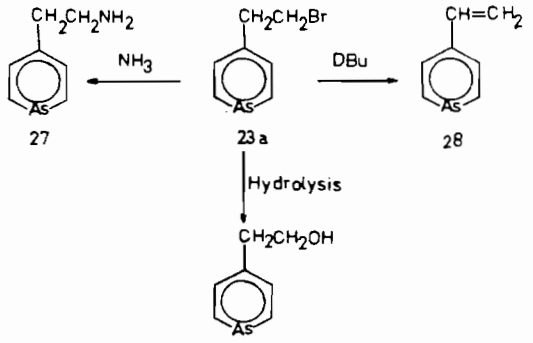


Scheme 7

4. Synthesis of amino-substituted arsabenzenes.

A. Synthesis of 4-(β-aminoethyl)arsabenzene and related compounds.

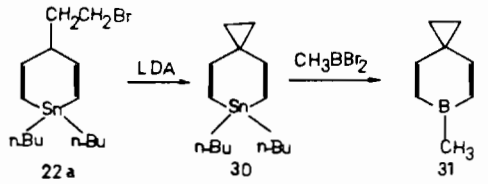
Compound 23a can be an ideal precursor for substituted arsabenzenes by carrying out several standard organic reactions (Scheme 8). The bromide (23a)



Scheme 8

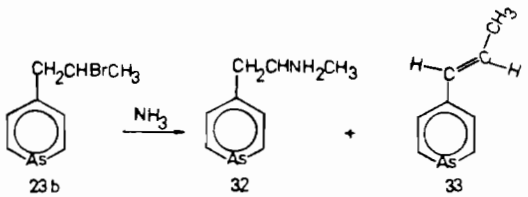
was reacted with anhydrous ammonia in methanol to afford 4-(β-aminoethyl) arsabenzene (27) in 60% yield. *In situ* treatment of Compound 22a with arsenic tribromide followed by DBU afforded a good yield of 4-vinylarsabenzene (28). 4-(β-hydroxyethyl)arsabenzene (29) was also formed by hydrolysis of Compound 23a in a dilute weak base (Abu-Orabi 1982).

One aspect of the synthetic potential of Compound 22a is that it was converted to 6,6-di-n-butyl-6-stannaspiro [2·5]octa-4,7-diene (30). Exchange of Compound 30 with methylboron dibromide afforded the boradiene, 6-methyl-6-boraspiro [2·5]-octa-4,7-diene (31) in 80% yield (Scheme 9) (Ashe *et al.* 1983). ^{13}C NMR and STO-3G calculations showed that the neutral boron analogue of the phenonium ion (31) has no extensive charge delocalization involving the cyclopropyl ring as it has been shown for related spiro-conjugated systems (Staley 1967; Staley *et al.* 1980).



Scheme 9

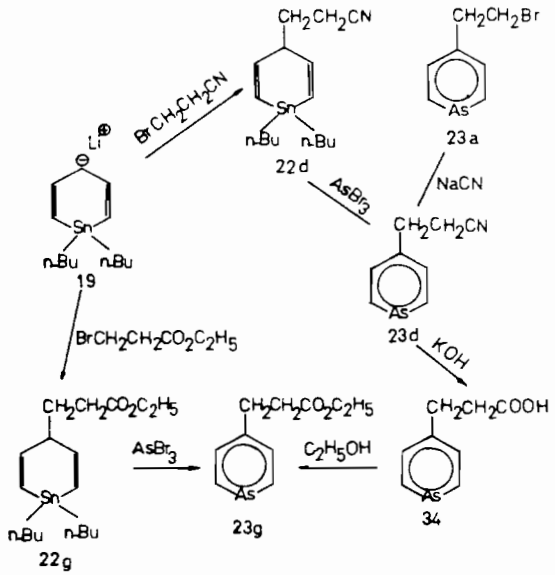
B. Synthesis of 4-(β-aminopropyl)arsabenzene.
We had hoped to convert Compound 23b to the amphetamine analogue, 4-(β-aminopropyl)arsabenzene (32) by using the same synthetic procedure for preparing 4-(β-aminoethyl)arsabenzene (27). The synthesis of Compound 32 appeared to offer difficulties since the elimination product was the predominant. Ninety percent of the reaction product was accounted for formation of 4-(trans-1-propenyl)arsabenzene (33) and only about 10% was characterized as the desired amine product (32) (Scheme 10) (Abu-Orabi 1982).



Scheme 10

C. Synthesis of 4-(2-amino-β-propionic acid) arsabenzene.
4-[(β-Ethoxycarbonyl)ethyl] arsabenzene (23g) is a very interesting compound since it can be converted to several important compounds by standard methods of organic chemistry. Scheme 11 gives an example of how to prepare this ester via several organic pathways. For example, reaction of the bromide (23a) with sodium cyanide in the presence of phase transfer catalyst such as

benzyl trimethyl ammonium chloride afforded the corresponding nitrile (23d) in good yield. Alternatively (23d) was prepared directly in 48% yield by the reaction of the stannacyclohexadienide (19) with 3-bromopropionitrile followed by treatment with arsenic tribromide (Abu-Orabi 1982). Basic hydrolysis of the nitrile (23d) afforded the corresponding carboxylic acid (34). Esterification of Compound 34 in anhydrous ethanol afforded 84% of the ester (23g). Alternatively, the ester (23g) was synthesized using the direct functionalization of 1,1-di-n-butyl-1-stannacyclohexadiene as mentioned in Scheme 6. The anion (19) was reacted with ethyl 3-bromopropionate to give 38% of 1,1-di-n-butyl-4-(β-carbethoxyethyl)stannacyclohexa-2,5-diene (22g) which subsequently was reacted with arsenic tribromide to afford 75% of the corresponding ester 23g.



Scheme 11

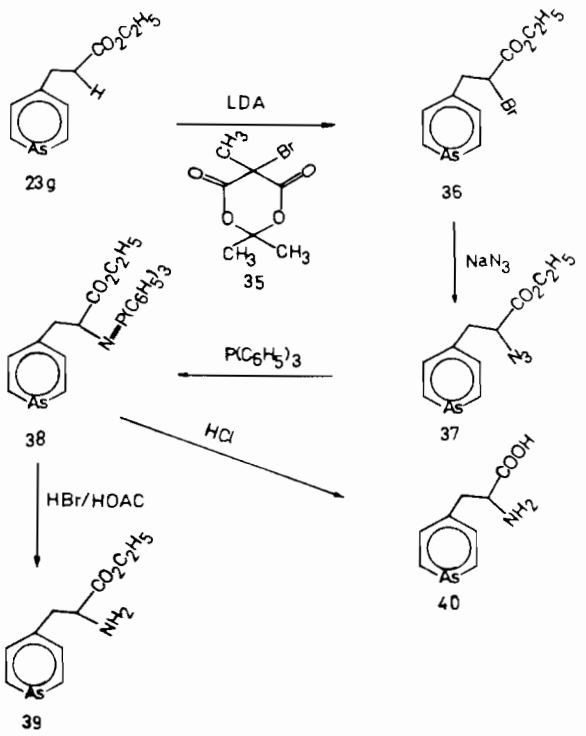
We had hoped to develop a synthesis of the arsabenzene analog of phenylalanine (40). The synthesis of this amino acid seems desirable since a radiolabelled derivative of this compound might be a useful radiopharmaceutical for radiodiagnosis of pancreas diseases (Counsell & Ice 1975).

The ester (23g) seems an ideal precursor for the synthesis of the amino acid (40) since there are several examples in the literature showing the synthesis of phenylalanine starting from ethyl 3-phenylpropionate (Horner & Gross 1955). Most of these methods could not be applied in the synthesis of Compound 40 because the arsabenzene ring is destroyed under electrophilic brominating conditions (Ashe *et al.* 1981) and is sensitive to strong bases (Ashe & Smith 1977; Maerkl *et al.* 1979).

Treatment of the ester (23g) with LDA followed by quenching with the mild brominating agent 5-bromo-2,2,5-trimethyl-1,3-dioxane-4,6-dione (35) afforded 55% of 4-[2-bromo-2-(ethoxycarbonyl)ethyl] arsabenzene (36)

(Scheme 12). This bromide is relatively stable and it can be easily stored under dry ice, but on heating or even standing at room temperature for a short period of time it turned into a dark colour due to decomposition (Ashe & Abu-Orabi 1983).

The conversion of the bromo ester (36) into the amino acid (40) was accomplished using a modification of Horner's methods for the preparation of phenylalanine (Horner & Gross 1955).



Scheme 12

The reaction of Compound 36 with sodium azide afforded 4-[2-azido-2-(ethoxycarbonyl)ethyl] arsabenzene (37), which was reacted with triphenylphosphine to give 4-[2-triphenylphosphineimino-2-(ethoxycarbonyl) ethyl] arsabenzene (38). Hydrolysis of Compound 38 in a mixture of aqueous hydrobromic acid and acetic acid followed by treatment with aqueous sodium bicarbonate afforded 30% of 4-[2-amino-2-(ethoxycarbonyl)ethyl] arsabenzene (39) (Ashe & Abu-Orabi 1983).

Alternatively, when the triphenylphosphineimino derivative (38) was hydrolyzed in aqueous hydrochloric acid, 4-(2-amino-β-propionic acid) arsabenzene (40) was obtained in 34% yield. The arsabenzene analog of phenylalanine (40) was characterized by the distinct violet colour of the ninhydrin colour test. The Rf value of the acid was measured in a mixture of pyridine, acetone, water and concentrated ammonium hydroxide in the relative ratio of 45 : 30 : 20 : 5, respectively and it was 0·52. This value was remarkably close

to that of phenylalanine (0·6) using the same conditions. The amino acid (40) was insoluble in all of the common organic solvents. However, a pure sample for the ^{1}H NMR was obtained by using preparative thin layer chromatography. The nonaromatic portion of the ^{1}H NMR spectrum of Compound 40 was virtually identical with that of phenylalanine (Abu-Orabi 1982).

DISCUSSION AND CONCLUSION

The physical and chemical properties of arsabenzene are very similar to those of benzene itself. Therefore, arsabenzene ring might serve as an isostere for the benzene ring in pharmaceutical drugs and other biologically active compounds. In order to develop a synthesis of substituted arsabenzenes and particulary to synthesize a few substituted target molecules which could be tested and studied from the point of view of their biological activities, we review the synthesis of 4-substituted arsabenzenes during the last two decades and also report on the synthesis of amino-substituted arsabenzenes (27) and (32) and the arsabenzene analog of phenylalanine (40).

4-(β-aminoethyl) arsabenzene (27) and 4-(β-aminopropyl) arsabenze (32) might have valuable biological activities, because both compound are the analogs of the β-phenyl ethylamine and amphetamine which are important in the treatment of some cases of schizophrenia.

The synthesis of arsabenzene analog of phenylalanine (40) might be suitable for incorporation of a radioisotope of arsenic which might allow tissue scanning of the pancreas and ultimately radiodiagnosis of pancreatic diseases. Neoplastic disease of the pancreas is usually detected only in the later stages of the disease when it is already too late. Therefore, early diagnosis would be highly desirable. One possible approach to this problem would involve the use of a radiopharmaceutical product which might accumulate in the pancreas and allow the organ to be externally photoscanned.

Compound 40 might be labelled with radioisotopes of arsenic like ^{73}As which is commercially available in the form of sodium arsenate solution that might be converted to $AsCl_3$ for incorporation in the synthesis of arsabenzene analog of phenylalanine (40), or ^{76}As which can be easily prepared by targetting ^{75}As in a nuclear reactor.

REFERENCES

Abu-Orabi, S.T. 1982. The syntheses of substituted arsabenzenes. Ph.D. thesis, University of Michigan, Ann Arbor, U.S.A.

Abu-Orabi, S.T. & Ashe, A.J., III. 1986. Diels-Alder reactions of arsabenzene. Proceedings of the Thirteenth Iraqi Chemical Conference, Irbil, Iraq.

Abu-Orabi, S.T. & Ashe, A.J., III. 1987. Diels-Alder reactions of arsabenzene. Journal of the Iraqi Chemical Society **12**: 117–35.

Ashe, A.J., III. 1971a. Phosphabenzene and arsabenzene. Journal of the American Chemical Society **93**: 3293–95.

Ashe, A.J., III. 1971b. Stibabenzene. Journal of the American Chemical Society **93**: 6690–91.

Ashe, A.J., III. 1978. The group 5 heterobenzenes. Accounts of Chemical Research **11**: 153–57.

Ashe, A.J., III. 1982. Group VA heterobenzenes: arsabenzene, stibabenzene and bismabenzene. Topics in Current Chemistry **105**: 125–55.

Ashe, A.J., III & Abu-Orabi, S.T. 1983. Preparation of 4-substituted arsabenzenes. Journal of Organic Chemistry **48**: 767–70.

Ashe, A.J., III, Abu-Orabi, S.T., Eisenstein, O. & Sandford, H.F. 1983. 6-Methyl-6-boraspiro[2·5]-octa-4, 7-diene, a boron analogue of the phenonium ion. Journal of Organic Chemistry **48**: 901–03.

Ashe, A.J., III & Chan, W.-T. 1975. The direction of the dipole moments of phosphabenzene and arsabenzene. Tetrahedron Letters **32**: 2749–52.

Ashe, A.J., III & Chan, W.-T. 1979. Preparation of 2-substituted arsabenzenes. Journal of Organic Chemistry **44**: 1409–13.

Ashe, A.J., III, Chan, W.-T. & Smith, T.W. 1978. Friedel-Crafts acylation of arsabenzene. Tetrahedron Letters **29**: 2537–40.

Ashe, A.J., III, Chan, W.-T., Smith, T.W. & Taba, K.M. 1981. Electrophilic aromatic substitution reactions of arsabenzene. Journal of Organic Chemistry **46**: 881–85.

Ashe, A.J., III, Diephouse, T.R. & El-Sheikh, M.Y. 1982. Stabilization of stibabenzene and bismabenzene by 4-alkyl substituents. Journal of the American Chemical Society **104**: 5693–99.

Ashe, A.J., III & Friedman, H.S. 1977. Pyrolysis of 1-arsabicyclo[2.2.2]triene derivatives. Tetrahedron Letters **15**: 1283–86.

Ashe, A.J., III & Gordon, M.D. 1972. Bismabenzene. The reaction of group V heteroaromatic compounds with hexafluorobutyne. Journal of the American Chemical Society **94**: 7596–97.

Ashe, A.J., III & Smith, T.W. 1977. The reaction of phosphabenzene, arsabenzene and stibabenzene with methyllithium. Tetrahedron Letters **5**: 407–10.

Counsell, R.E. & Ice, R.D. 1975. The design of organ-imaging radiopharmaceuticals. In: **Arens, E.J. & Arens, E.D. (Eds).** Drug design, vol. 6, Academic Press, New York.

Hodges, R.V., Beauchamp, J.L., Ashe, A.J., III & Chan, W.-T. 1985. Proton affinities of pyridine, phosphabenzene and arsabenzene. Organometallics **4**: 457–61.

Horner, L. & Gross, A. 1955. Die Verwendung der Phosphin-imine zur Einfuhrung primarer Aminogruppen. Justus Liebigs Annalen der Chemie **591**: 117–34.

Jutzi, P. & Baumgartner, J. 1978. Synthese und Reaktionen von Element-IV B-substituierten Stannacyclohexadienderivaten. Journal of Organometallic Chemistry **148**: 247–55.

Maerkl, G., Baier, H. & Heinrich, S. 1975. 4-Hydroxyarsabenzene: An Arsaphenol. Angewandte Chemie International Edition **14**: 710–11.

Maerkl, G., Bergbauer, A. & Rampal, J.B. 1983. 2-Aryl-^{3}-arsenine, 2,6-diaryl-^{3}-arsenine, 2-aryl-4-R-^{3}-arsenine und 2,4,6-triaryl-^{3}-arsenine durch 4-hydroxy-1,4-dihydro-arsenin → arsenin-Unlagerung. Tetrahedron Letters **24**: 4079–82.

Maerkl, G., Hollriegl, H. & Schlosser, W. 1984. Silacyclohexa-dienylanionen. Bis- und tris-(trimethylsilyl)-silacyclohexadiene. Journal of Organometallic Chemistry **260**: 129–70.

Maerkl, G. & Kneidl, F. 1973. Simple synthesis of 4-monosubstituted arsa- and phosphabenzenes. Angewandte Chemie International Edition **12**: 931–32.

Maerkl, G. & Kneidl, F. 1974. 4-Alkoxy-arsabenzenes. Angewandte Chemie International Edition **13**: 667–69.

Maerkl, G. & Rampal, J.B. 1977. Umlagerung und Dimerisierung von 1-R-1-arsa-4-methylencyclohexadienen-2,5 zu arsabenzene. Tetrahedron Letters **30**: 2569–72.

Maerkl, G., Rampal, J.B. & Schoberl, V. 1979. Arsabenzaldehyd Umsetzung mit Kohlenstoff-und Stickstoff-nucleophilen Arsazimtsaure Arsabenzonitril. Tetrahedron Letters **34**: 3141–44.

Quin, L.D. 1981. The heterocyclic chemistry of phosphorus. Wiley Interscience, New York.

Staley, S.W. 1967. On the thermodynamic significance of delocalization in dienes. Thermodynamics of the vinylcyclopropyl system. Journal of the American Chemical Society **89**: 1532–33.

Staley, S.W., Howard, A.E., Harmony, M.D., Mathur, S.N., Kattija-Ari, M., Choe, J.-I. & Lind, G. 1980. Microwave spectrum, dipole moment, and structure of spiro [2·4]hepta-4,6-diene. Evidence for significant cyclopropyl conjugation. Journal of the American Chemical Society **102**: 3639–40.

Tzschach, A. & Heinicke, J. 1978. Arsenheterocyclen. VEB Deutscher Verlag für Grundstoffindustrie, Leipzig.

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حول تحضير مشتقات زرنيخ البنزين

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